Exhibit 8

UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF NEW YORK

IN RE: Acetaminophen – ASD–ADHD Products Liability Litigation **This Document Relates To: All Actions**	**22-md-3043 (DLC)**

RULE 26 REBUTTAL EXPERT REPORT OF ROBERT M CABRERA, PhD

I have examined all the expert reports presented by the Defendants on July 21, 2023, and I am now submitting this rebuttal report in accordance with Rule 26. The purpose of this report is to address the most inaccurate opinions and statements presented by the Defendants' experts, though it is not intended to encompass every point of contention. My primary focus lies on countering the assertions made in the report of Dr. Wendy Chung, but I will also note that the erroneous positions advocated by Dr. Chung are similarly mirrored in the reports of other Defendants' experts. Therefore, the disagreements I outline below pertain to all the expert reports provided by the Defendants, despite my specific reference to Dr. Chung's report. Additionally, I have thoroughly reviewed and concur with the rebuttal reports presented by other Plaintiffs' experts, which have addressed various other criticisms and issues in this matter.

One of the founders of modern teratology, James Wilson, wrote in Environment and Birth Defects (1973),

> …in 1900, 36 years after the Austrian monk Gregor Mendel first enunciated them, the principles of genetics were rediscovered. It was quickly assumed that genes that control normal development could also determine abnormal development. In the ensuing 50 years the tendency to attribute all human developmental errors to this cause became deeply ingrained in medicine. Like many another generalization with some basis of fact, this one offered the convenience of ready explanation without requiring rigorous proof. Thus, teratology during the early part of the present century again found itself with less than an objective outlook, this time not under the sway of superstition and fancy but owing to the overextension of a scientific principle. (p.10)

A review of Dr. Chung's report offers the same type of genetic causality warned about 50 years ago by Wilson regarding birth defects. Dr. Chung exclusively focuses on genetic etiologies, providing "the convenience of ready explanation without requiring rigorous proof" to explain neurobehavioral pathologies (functional deficits). Wilson also described four manifestations of deviant development or developmental toxicity: (1) death, (2) malformations, (3) small for gestational age, and (4) functional deficits. Neurobehavioral teratology focuses specifically on functional deficits, neuropathology, and neurobehavioral disorders, including ADHD and ASD.

Genetics and genomics have moved teratology and biological sciences towards "-omics[1]" data over the last two decades, but the absolute omission of environmental causes of birth defects by Dr. Chung is "less than an objective outlook" on ASD, ADHD, and teratology.

Dr. Chung claims, "ASD is a neurodevelopmental condition marked by persistent deficits in social communication and interaction, and restricted, repetitive patterns of behaviors, interests, or activities. ADHD is a different neurodevelopmental disorder with a distinct etiology and diagnosis." (Chung, p.2, para. 3.i.). The first part of that statement is true. ADHD and ASD are different neurodevelopmental disorders, but these disorders also overlap in presentation and etiology. It is clinically recognized that patients with ASD often meet the criteria for ADHD and ASD. In the past, The Diagnostic and Statistical Manual-4th Edition (DSM-4) indicated ASD diagnosis was an exclusion criterion for ADHD, but the DSM-5 (5th Edition, 2013) stopped prohibiting such comorbid diagnosis ten years ago:

> Despite the growing body of research pointing at the frequent co-occurrence of these two disorders, the previous DSM-IV-TR has not allowed a dual diagnosis. The DSM-V, in its revised ADHD diagnostic criteria, recognizes the frequency of this co-occurrence and allows, for the first time, a co-morbid diagnosis of ADHD with autism spectrum disorder.[2]

Dr. Chung's position is odd, as even an untrained observer could appreciate that the repetitive and restricted behaviors of ASD overlap with the hyperactive and impulse control problems of ADHD. A medical doctor in this field would and should be familiar with the DSM-5 and this allowance. This is meaningful for the educator and medical practitioner, because beyond behavioral testing and DSM-V coding, ASD and ADHD overlap at phenotypic, genetic, and environmental levels. Clinically it is recognized that these conditions co-occur, such that 28-44% of individuals with ASD also present with ADHD, reviewed by Lai et al.[3] Moreover, these conditions have overlapping **genetic and environmental** etiologies as described below.

Regarding a genetic etiology or etiologies for ASD and ADHD, Dr. Chung indicates, "Genetic variants account for most known causes of ASD and ADHD." (Chung, p. 3, para. 3.ii). Her report repeatedly references sibling-based and twinning studies, including Tick et al.[4] (2016), a meta-analysis, and Taylor et al.[5] (2020), based on two nationwide Swedish twin cohorts. Tick et al. reported on all selected studies, using fixed thresholds as reported in each study, which resulted in a heritability of 74% (95% CI 0.70–0.87), with a significant proportion of shared environmental

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[1] Many areas of research can be classified as omics. Examples include proteomics, transcriptomics, genomics, metabolomics, lipidomics, and epigenomics, which correspond to global analyses of proteins, RNA, genes, metabolites, lipids, and methylated DNA or modified histone proteins in chromosomes, respectively. Committee on the Review of Omics-Based Tests for Predicting Patient Outcomes in Clinical Trials; Board on Health Care Services; Board on Health Sciences Policy; Institute of Medicine; Micheel CM, Nass SJ, Omenn GS, editors. Washington (DC): National Academies Press (US); 2012 Mar 23.

[2] Leitner Y. The co-occurrence of autism and attention deficit hyperactivity disorder in children - what do we know? Front Hum Neurosci. 2014 Apr 29;8:268. doi: 10.3389/fnhum.2014.00268. PMID: 24808851; PMCID: PMC4010758.

[3] Lai MC, Lombardo MV, Baron-Cohen S. Autism. Lancet. 2014 Mar 8;383(9920):896-910. doi: 10.1016/S0140-6736(13)61539-1. Epub 2013 Sep 26. PMID: 24074734.

[4] Tick et al. Heritability of autism spectrum disorders: a meta-analysis of twin studies. J Child Psychol Psychiatry. 2016 May;57(5):585-95. doi: 10.1111/jcpp.12499. Epub 2015 Dec 27. PMID: 26709141; PMCID: PMC4996332.

[5] Taylor et al. Etiology of Autism Spectrum Disorders and Autistic Traits Over Time. JAMA Psychiatry. 2020 Sep 1;77(9):936-943. doi: 10.1001/jamapsychiatry.2020.0680. PMID: 32374377; PMCID: PMC7203675.

effects: 25% (95% CI 0.12–0.37). Taylor et al. report that across birth cohorts, the heritability of clinical diagnosis of ASD was 0.93, the heritability of broad screening diagnoses of ASD was 0.82, and the heritability of autistic traits was 0.61 to 0.73. Taylor et al. also report that their results concur with Tick et al. with strong heritability and a modest role for the environment across studies. Dr. Chung reports, "Genetic variants account for most known causes of ASD and ADHD." (Chung, p. 3, para. 3.ii). On page 27, Dr. Chung suggests, "In aggregate, the contribution of common variants is estimated to account for approximately 50% of the risk of ASD (Klei 2021, Gaugler 2014). Rare inherited variants contribute approximately 35% of the risk of ASD. De novo mutations contribute the remaining 15%, approximately." (Chung, p. 27, para. 63). This is the genetic component of ASD, but Dr. Chung has omitted the environmental component. Dr. Chung's report differs from gene-environmental interactions identified in Taylor et al., Tick et al., and her 2014 Ted talk, where she clearly states regarding genetics, "I'm focusing on this not because genes are the only cause of autism, but it's a cause of autism that we can readily define and be able to better understand the biology…". Likewise, in scientific publications on ASD, such as the one titled *Insufficient Evidence for "Autism-Specific" Genes*, Dr. Chung as a co-author reported, "The neurodevelopmental phenotype, whether pathological or not, depends on the profile of quantitative deleterious effects associated with the rare variant, other sources of genetic variation such as polygenic and oligogenic background risk, and environmental and stochastic variation."[6] The statements in paragraph 3. ii. of her expert report are (1) not consistent with Dr. Chung's Ted talk, (2) not consistent with her scientific work in the field of ASD, and (3) not consistent with the references she uses to estimate heritability.

The modeling of gene-environment interactions is common in the field of genetics and population genetics. The modeling of phenotypic variance (Vp) = genetic variance (Vg) + environmental variance (Ve), and heritability is the proportion of genetic variance over phenotypic variance (Vg/Vp), which can also be written as Vg/(Vg+Ve). Understanding and applying this model, the objective and literal textbook answer-conclusion should be, that a monozygotic concordance rate that is less than 98-100% means that environmental factors influence the phenotype. For example, monozygotic twins are expected to have near unity (0.98-1.0) concordance in genetically caused phenotypes or pathologies. For example, eye color is reported to have 0.98 concordance in monozygotic twins, with 0.49 concordance in dizygotic twins.[7] Polderman et al.[8], a co-occurrence study of ASD and ADHD in 17,770 twins, models gene-environment interactions, as do most studies in this field. Specifically, they examined "whether additive genetic, dominant genetic and shared and non-shared environmental factors contributed significantly to the total variance of ASD and ADHD dimensions." They conclude there are both genetic and environmental factors that influence overlapping dimensions of ADHD and ASD. Specifically, ASD repetitive behaviors were correlated with both ADHD inattention (0.39 in males and 0.33 in females) and ADHD hyperactivity/impulsivity (0.40 in both males and females). Dr. Chung presents a 77% concordance

[6] Myers et al. Insufficient Evidence for "Autism-Specific" Genes. Am J Hum Genet. 2020 May 7;106(5):587-595. doi: 10.1016/j.ajhg.2020.04.004. Epub 2020 Apr 30. PMID: 32359473; PMCID: PMC7212289.

[7] Bito et al. Eye color changes past early childhood. The Louisville Twin Study. Arch Ophthalmol. 1997 May;115(5):659-63. doi: 10.1001/archopht.1997.01100150661017. PMID: 9152135.

[8] Polderman et al. The co-occurrence of autistic and ADHD dimensions in adults: an etiological study in 17,770 twins. Transl Psychiatry. 2014 Sep 2;4(9):e435. doi: 10.1038/tp.2014.84. PMID: 25180574; PMCID: PMC4203013.

of ASD in monozygotic twins in her Ted talk, estimated as 77-88% in her expert report, which still falls short of expectations for a strictly genetic phenotype or a genetic or neurogenetic disease. Dr. Chung acknowledges this with another odd statement, "Importantly, the lack of 100% concordance between monozygotic twins does not necessarily support a role for non-genetic factors in the etiology of ASD." (Chung, p. 24, para. 55). Dr. Chung then suggests, "discordance could be explained by the failure or lack of diagnosis of the "unaffected" twin." (Chung, p. 24, para. 55). In the twinning studies cited by Dr. Chung, the heritability of phenotypes and genetic diseases occur and are modeled in the context of environmental risks and gene–environment interactions. Identical twins in all these studies are monozygotic-genetically, with the same parents, in the same environment, with likely the same doctors (pediatricians) up until the point of diagnosis, but Dr. Chung proposes diagnostic failure for the discordance. The answer is there, but hidden, "Heritability is the fraction of the variability of the phenotype that is due to inherited genetic factors." (p. 20) That is the written description of Vg / Vp, where Vp = Vg + Ve. While diagnostic failures do happen, the observed discordance has a textbook explanation, based firmly on genetic models: phenotypic variability (Vp) is a function of genetic variability (Vg) and environment factor variability (Ve).[9] An example of phenotypic variation easily observed in humans explained by this equation is height. The total phenotypic variance in height within a population can be determined by variance due to genetic differences among individuals (Vg) and the variance due to differences in environmental factors (Ve), such as nutrition and health. Studies have estimated the heritability of height in humans is ~0.8, so (Vp) = ~0.8 (Vg) + ~0.2(Ve).10

Regarding ASD and ADHD, Polderman et al.[8] also report twin correlations by dimension range from 0.31-0.40, which leaves considerable room for environmental or unknown factors. While Chung offers a genetic model in the absence of other factors, Polderman et al. propose a standard statistical model that supports genetic and environmental factors contributing to various and overlapping dimensions of ADHD and ASD. The authors report a comparison of genetic and environmental correlations with four of six dimensional interactions being stronger for environmental interactions for ADHD and ASD versus genetic interactions.

Regarding the overlapping genetic etiologies of ASD and ADHD, Satterstrom et al. reported ASD and ADHD have a similar burden of rare protein-truncating variants.[11] Comparing ASD or ADHD cases to controls indicates that ASD versus ADHD is not statistically different regarding protein-truncating variants (PTV), but both diseases are significantly different from controls in this regard (see Table 3 in the referenced study). Table 4 of this study reports 15 common genes, supporting an overlapping genetic etiology, with PTV. One of the genes, SLC2A14, has also been reported to interact with acetaminophen, with decreased expression in human hepatocytes.[12] It is worth noting

[9] Strachan, T., & Read, A. (2000). Human Molecular Genetics (2nd ed.). John Wiley & Sons. (p. 450)
[10] Yang et al. Common SNPs explain a large proportion of the heritability for human height. Nat Genet. 2010 Jul;42(7):565-9. doi: 10.1038/ng.608. Epub 2010 Jun 20. PMID: 20562875; PMCID: PMC3232052.
[11] Satterstrom et al. Autism spectrum disorder and attention deficit hyperactivity disorder have a similar burden of rare protein-truncating variants. Nat Neurosci. 2019 Dec;22(12):1961-1965. doi: 10.1038/s41593-019-0527-8. Epub 2019 Nov 25. PMID: 31768057; PMCID: PMC6884695.
[12] Yu et al. Multiple microRNAs function as self-protective modules in acetaminophen-induced hepatotoxicity in humans. Arch Toxicol. 2018 Feb;92(2):845-858. doi: 10.1007/s00204-017-2090-y. Epub 2017 Oct 24. PMID: 29067470; PMCID: PMC5820133.

that SLC2A14 transports the oxidized form of vitamin C, dehydroascorbic acid, and glucose. Vitamin C is an antioxidant and is reported to exert a protective effect against acetaminophen-induced hepatotoxicity.[13] SLC2A14 is also predominately expressed in testis, but the acetaminophen interaction was based on human liver cells, which may not extrapolate directly to neuro-developmental or reproductive toxicity, so additional studies are needed to detect and delineate any mechanistic interactions between acetaminophen, SLC2A14, ASD, and ADHD.

There are also other reported common ASD and ADHD gene interactions, which include acetaminophen-gene-disease interactions. This is consistent with the approach applied by Santos et al.[14] For example, data extracted from the Comparative Toxicogenomics Database indicates 12 genes interact with both acetaminophen and ADHD, and 273 genes are reported to interact with acetaminophen and ASD, with three genes reported to interact with acetaminophen, ASD, and ADHD. These genes are capicua (CIC), catechol-O-methyltransferase (COMT), and steroid sulfatase (STS).

CIC was reported to interact with acetaminophen in a multicenter study of acetaminophen toxicity.[15] This multicenter study was based on murine hepatotoxicity, which may not extrapolate directly to neurotoxicity, but NAPQI has demonstrated dose-dependent toxicity in both the brain and liver of various mouse models. CIC has also been characterized in mice and humans. Briefly, a genetic mutation in CIC, identified in a patient, was used by members of the Finnell Cabrera laboratory to produce a humanized mouse model carrying the same mutation.[16] The mice demonstrated hyperactivity, impaired learning and memory, and neural (cortical) layering defects. In total, five individuals with *de novo* heterozygous truncating mutations in CIC were found with similar clinical features, including intellectual disability, ADHD, and ASD. This is one example of the many genes altered by acetaminophen, where deleterious *de novo* mutations have been detected in patients with ASD and ADHD.

Both COMT and STS genes were also reported by Santos et al. concerning alterations by APAP.[14] A small clinical study of six women reported that steroid sulfation (STS) is reduced by acetaminophen.[17] Loss of STS in humans results in X-linked ichthyosis (XLI).[18] XLI or STS

[13] Kurahashi et al. Ascorbic acid prevents acetaminophen-induced hepatotoxicity in mice by ameliorating glutathione recovery and autophagy. Arch Biochem Biophys. 2016 Aug 15;604:36-46. doi: 10.1016/j.abb.2016.06.004. Epub 2016 Jun 7. PMID: 27288086.

[14] Santos et al. A Role for Gene-Environment Interactions in Autism Spectrum Disorder Is Supported by Variants in Genes Regulating the Effects of Exposure to Xenobiotics. Front Neurosci. 2022 May 19;16:862315. doi: 10.3389/fnins.2022.862315. PMID: 35663546; PMCID: PMC9161282.

[15] Beyer et al. Multicenter study of acetaminophen hepatotoxicity reveals the importance of biological endpoints in genomic analyses. Toxicol Sci. 2007 Sep;99(1):326-37. doi: 10.1093/toxsci/kfm150. Epub 2007 Jun 11. PMID: 17562736.

[16] Lu et al. Disruption of the ATXN1-CIC complex causes a spectrum of neurobehavioral phenotypes in mice and humans. Nat Genet. 2017 Apr;49(4):527-536. doi: 10.1038/ng.3808. Epub 2017 Mar 13. PMID: 28288114; PMCID: PMC5374026.

[17] Rogers et al. Paracetamol interaction with oral contraceptive steroids: increased plasma concentrations of ethinyloestradiol. Br J Clin Pharmacol. 1987 Jun;23(6):721-5. doi: 10.1111/j.1365-2125.1987.tb03107.x. PMID: 3111513; PMCID: PMC1386167.

[18] Jöbsis et al. X-linked ichthyosis and X-linked placental sulfatase deficiency: a disease entity. Histochemical observations. Am J Pathol. 1980 May;99(2):279-89. PMID: 6929654; PMCID: PMC1903491.

deficiency is also associated with ADHD and ASD in humans[19] and mouse models with deletion of STS show ADHD core behaviors.[20] Four different rat studies examining hepatotoxicity and nephrotoxicity have confirmed and reported that APAP reduces COMT expression.[21] In genetic-animal models of COMT function, COMT is reported to metabolize dopamine (neurotransmitter) into 3-methoxytyramine, the major metabolite of released dopamine in rat brain (prefrontal cortex).[22] COMT is associated with ASD and ADHD in mouse mutant models[23] and variations are clinically associated with ADHD and response to ADHD medication.[24] Despite COMT being one of the most characterized genes associated with ADHD, a recent meta-analysis did not support this association.[25] The authors of this meta-analysis conclude, "ADHD does not stem from errors in a single variation but from additive effects of defects in more than one gene, multiple genetic interactions, and gene–environment interactions."

On page 3 of her report at paragraph 3.v., Dr. Chung states, "There is no reliable scientific evidence that acetaminophen changes expression in the human brain," but I will add that gene expression analyses in living human brains or human embryonic-fetal brains are not the subject of any drug interaction studies. Even with modern instruments, the invasiveness of such experiments would be deemed unethical if not unlawful. Even without such experiments, we know valproic acid (VPA) causes birth defects in animals and humans, and we know VPA causes ASD in humans and is used to model ASD in mice. No such "human brain" experiments were required for VPA, and requiring

[19] Kent et al. X-linked ichthyosis (steroid sulfatase deficiency) is associated with increased risk of attention deficit hyperactivity disorder, autism and social communication deficits. J Med Genet. 2008 Aug;45(8):519-24. doi: 10.1136/jmg.2008.057729. Epub 2008 Apr 15. PMID: 18413370.

[20] Trent et al. Steroid sulfatase-deficient mice exhibit endophenotypes relevant to attention deficit hyperactivity disorder. Psychoneuroendocrinology. 2012 Feb;37(2):221-9. doi: 10.1016/j.psyneuen.2011.06.006. Epub 2011 Jul 1. PMID: 21723668; PMCID: PMC3242075.

[21] Rawls et al. Predicting changes in renal metabolism after compound exposure with a genome-scale metabolic model. Toxicol Appl Pharmacol. 2021 Feb 1;412:115390. doi: 10.1016/j.taap.2020.115390. Epub 2020 Dec 31. PMID: 33387578; PMCID: PMC7859602; Pannala et al. Mechanism-based identification of plasma metabolites associated with liver toxicity. Toxicology. 2020 Aug;441:152493. doi: 10.1016/j.tox.2020.152493. Epub 2020 May 30. PMID: 32479839; Suzuki et al. In vitro gene expression analysis of hepatotoxic drugs in rat primary hepatocytes. J Appl Toxicol. 2008 Mar;28(2):227-36. doi: 10.1002/jat.1328. PMID: 18246545; Morishita et al. Gene expression profile in liver of differing ages of rats after single oral administration of acetaminophen. J Toxicol Sci. 2006 Dec;31(5):491-507. doi: 10.2131/jts.31.491. PMID: 17202762.

[22] Karoum et al. 3-Methoxytyramine is the major metabolite of released dopamine in the rat frontal cortex: reassessment of the effects of antipsychotics on the dynamics of dopamine release and metabolism in the frontal cortex, nucleus accumbens, and striatum by a simple two pool model. J Neurochem. 1994 Sep;63(3):972-9. doi: 10.1046/j.1471-4159.1994.63030972.x. PMID: 7914228.

[23] Gogos et al. Catechol-O-methyltransferase-deficient mice exhibit sexually dimorphic changes in catecholamine levels and behavior. Proc Natl Acad Sci U S A. 1998 Aug 18;95(17):9991-6. doi: 10.1073/pnas.95.17.9991. PMID: 9707588; PMCID: PMC21449; Papaleo et al. Genetic dissection of the role of catechol-O-methyltransferase in cognition and stress reactivity in mice. J Neurosci. 2008 Aug 27;28(35):8709-23. doi: 10.1523/JNEUROSCI.2077-08.2008. PMID: 18753372; PMCID: PMC2561993.

[24] Eisenberg Jet al. Haplotype relative risk study of catechol-O-methyltransferase (COMT) and attention deficit hyperactivity disorder (ADHD): association of the high-enzyme activity Val allele with ADHD impulsive-hyperactive phenotype. Am J Med Genet. 1999 Oct 15;88(5):497-502. PMID: 10490706.

[25] Sun et al. Role of COMT in ADHD: a systematic meta-analysis. Mol Neurobiol. 2014 Feb;49(1):251-61. doi: 10.1007/s12035-013-8516-5. Epub 2013 Aug 2. PMID: 23907791.

or proposing such unethical experiments as a burden of proof for any other medication or environmental exposure is unreasonable.

In the same paragraph, Dr. Chung goes on to state, "There are also no data or study suggesting that some sort of genetic susceptibility to acetaminophen detoxification causes ASD or ADHD among individuals prenatally exposed to acetaminophen." (Chung, p. 3, para. 3.v.). There are gene-drug interactions with acetaminophen as there are gene-drug interactions with ASD and ADHD, and there is overlap here regarding etiology as well. For example, several lines of evidence support that oxidative stress is an underlying interaction for the observed associations between genetic, immunological, and environmental factors with autism. see review titled *How environmental and genetic factors combine to cause autism: A redox/methylation hypothesis*.[26] This review indicates that heavy metals such as mercury lower glutathione (GSH), consistent with the Adverse Outcome Pathway for mercury and acetaminophen presented in my report (Cabrera, p. 35)[27]. It also indicates GSH/GSSG redox influences cellular activities, including proliferation and differentiation, which is likewise consistent with the effect of reducing and oxidative environments on cell proliferation, differentiation, apoptosis, and necrosis presented in my report (Cabrera, p. 63). This review also supports that xenobiotics are conjugated to GSH directly or by glutathione-S-transferase-catalyzed reactions. As indicated in my report, "The primary proteins NAPQI is reported to interact with are glutathione S-transferases." (Cabrera, p. 43) It should come as no surprise that there are interactions between glutathione-S-transferases (GSTs) and ASD.

Two initial studies in 2006 reported an association between a GST null allele and autism, suggesting that GSTs contribute to the risk of oxidative stress and autism.[28] This was followed up by another study in 2019 that reported that GST polymorphisms including the GSTM1 "active genotype" decreased the risk of ASD (OR = 0.554, 95%CI: 0.313–0.983, p = 0.044), and the GSTA1 CC genotype increases susceptibility to ASD (OR = 4.132, 95%CI: 1.219–14.012, p = 0.023).[29] Gene-gene interactions between GSTM1 active and GSTT1 active genotypes also decreased the risk of ASD (OR = 0.126, 95%CI: 0.029–0.547, p = 0.006), as did GSTT1 active and GSTP1 llelle (OR = 0.170, 95%CI: 0.029–0.992, p = 0.049). This study also reported an increased risk of ASD with GSTM1 active and GSTP1 llelle (OR = 11.088, 95%CI: 1.745–70.456, p = 0.011).

[26] Deth Ret al. How environmental and genetic factors combine to cause autism: A redox/methylation hypothesis. Neurotoxicology. 2008 Jan;29(1):190-201. doi: 10.1016/j.neuro.2007.09.010. Epub 2007 Oct 13. PMID: 18031821.
[27] Page numbers correspond to Cabrera amended report (June 22, 2023).
[28] Buyske et al. Analysis of case-parent trios at a locus with a deletion allele: association of GSTM1 with autism. BMC Genet. 2006 Feb 10;7:8. doi: 10.1186/1471-2156-7-8. PMID: 16472391; PMCID: PMC1382247; James et al. Metabolic endophenotype and related genotypes are associated with oxidative stress in children with autism. Am J Med Genet B Neuropsychiatr Genet. 2006 Dec 5;141B(8):947-56. doi: 10.1002/ajmg.b.30366. PMID: 16917939; PMCID: PMC2610366.
[29] Mandic-Maravic et al. Interaction of glutathione S-transferase polymorphisms and tobacco smoking during pregnancy in susceptibility to autism spectrum disorders. Sci Rep. 2019 Mar 1;9(1):3206. doi: 10.1038/s41598-019-39885-w. PMID: 30824761; PMCID: PMC6397281.

The same research group also published a study titled, *Glutathione S-Transferase Polymorphisms and Clinical Characteristics in Autism Spectrum Disorders* and reported,[30]

> Recent findings suggested that oxidative stress and genetic variability in glutathione S transferases (GSTs) might increase the risk of ASD development. We aimed to determine whether GST polymorphisms influence the severity of symptoms as well as the cognitive and adaptive abilities in children with ASD.

The study used Autism Diagnostic Interview-Revised (ADI-R) scores for assessment of signs of ASD. The study was performed as a cross-sectional study involving 113 ASD patients (92 males, 21 females, 9.36 ± 5.88 years old). Results from the study indicate that with maternal medication use during pregnancy, the GSTA1∗CC genotype was significantly predictive of a lower ADI-R D score in children. In cases where the mother had not used any medication during pregnancy, the GSTA1∗CC genotype was significantly predictive of a higher ADI-R D score. It is well established that acetaminophen is one of the most frequently used medications in pregnancy, but other reported medications included antibiotics and antihypertensives.

Dr. Chung discusses polygenic risk scores in her report, but this is once again only half the science, as genetics is only half of the equation for phenotypic variability. The more appropriate utility and interpretation of polygenic risk scores are "genetic susceptibility for complex conditions should not be viewed in isolation but be considered along with lifestyle and environmental factors in the multivariate evaluation of disease risk."[31]

Dr. Chung goes so far as to defend thalidomide, misoprostol, and valproic acid. Dr. Chung reports, "Studies, including genetic studies, are on-going to investigate these associations and potential confounding by genetics." (Chung, p. 28, para. 68). Defending these chemicals is akin to defending war criminals; these chemicals are not merely associated with ASD, these chemicals are *known* human teratogens, i.e., they have caused congenital malformations and functional deficits in humans. Thalidomide caused crippling defects in an estimated 8,000 children, born with phocomelia, in the span of two years, and it is foundational to the field of modern teratology. Fetal thalidomide syndrome is characterized by abnormalities of the craniofacial structures, limbs, and internal organs.[32] Misoprostol can be used to induce labor, but it is also used in combination with another medication to induce medical abortions. Used alone and often inappropriately in areas where access to medical terminations of pregnancies is otherwise illegal, misoprostol has traumatized numerous mothers and maimed and malformed their babies that survived failed terminations. Reported results from a meta-analysis on misoprostol indicate risks of congenital anomalies related to misoprostol were supported for any congenital defect (OR=3.56; 95% CI: 0.98-12.98), Möbius sequence (OR=25.31; 95% CI: 11.11-57.66) and terminal transverse limb

[30] Mandic-Maravic et al. Glutathione S-Transferase Polymorphisms and Clinical Characteristics in Autism Spectrum Disorders. Front Psychiatry. 2021 Jun 25;12:672389. doi: 10.3389/fpsyt.2021.672389. PMID: 34248709; PMCID: PMC8267579.

[31] Torkamani et al. The personal and clinical utility of polygenic risk scores. Nat Rev Genet. 2018 Sep;19(9):581-590. doi: 10.1038/s41576-018-0018-x. PMID: 29789686.

[32] Smithells and Newman. Recognition of thalidomide defects. J Med Genet. 1992 Oct;29(10):716-23. doi: 10.1136/jmg.29.10.716. PMID: 1433232; PMCID: PMC1016130.

defects (OR=11.86; 95% CI: 4.86-28.90).[33] Valproic acid is associated with a 10-fold increase in neural tube defects (NTD) risk and is also associated with genitourinary and musculoskeletal anomalies, cleft lip and/or palate, and congenital heart defects. A recent meta-analysis of VPA-associated malformation reported a 2-7-fold higher risk of congenital malformations compared to other antiepileptic drugs.[34] As reviewed by Lanrigan,[35]

> Indirect evidence for an environmental contribution to autism comes from studies demonstrating the sensitivity of the developing brain to external exposures such as lead, ethyl alcohol and methyl mercury. But the most powerful proof-of-concept evidence derives from studies specifically linking autism to exposures in early pregnancy - thalidomide, misoprostol, and valproic acid; maternal rubella infection; and the organophosphate insecticide, chlorpyrifos.

Gene-drug interactions do indeed modify adverse risks for these and other medications, as I have personally examined and identified genetic modifiers of NTD risk due to *in utero* valproic acid exposures.[36] Despite our ability to reduce risk via genetic modifiers or antioxidants, this in no way exonerates these medications from the teratogenic dangers they pose to embryos and fetuses.

Regarding points 3.vii a-d on page 4 of Dr. Chung's report, these criticisms are general to the state of science. For example, residual confounding is always present, even in the most well-designed observational studies. It is likewise true that we can predict the average rate and types of *de novo* mutations, but we cannot predict the locations or genes that may be mutated *a priori.* Finally, if any event is exceedingly rare in science, such as rare or novel *de novo* mutations, they cannot be fit to statistical models. Our statistical methods deal well with common alleles or occurrences, and we can identify the outliers, but modeling rare events is difficult because they are unexplained or uncommon to our models. Nevertheless, we can draw conclusions when gene mutations or chemical exposures increase the frequency of an event above background or control rates. This is how we know thalidomide, misoprostol, and valproic acid are human teratogens even in the absence of double-blind case-control clinical studies in pregnant women to determine teratogenic outcomes. I will also note that Sir Austin Bradford Hill had no genetic studies; he nevertheless drew sound conclusions based on the totality of longitudinal evidence available regarding the causal relation between cigarette smoking and lung cancer.

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[33] da Silva Dal Pizzol et al. Prenatal exposure to misoprostol and congenital anomalies: systematic review and meta-analysis. Reprod Toxicol. 2006 Nov;22(4):666-71. doi: 10.1016/j.reprotox.2006.03.015. Epub 2006 Jun 5. PMID: 16750609.

[34] Tanoshima et al. Risks of congenital malformations in offspring exposed to valproic acid in utero: A systematic review and cumulative meta-analysis. Clin Pharmacol Ther. 2015 Oct;98(4):417-41. doi: 10.1002/cpt.158. Epub 2015 Aug 10. PMID: 26044279.

[35] Landrigan. What causes autism? Exploring the environmental contribution. Curr Opin Pediatr. 2010 Apr;22(2):219-25. doi: 10.1097/MOP.0b013e328336eb9a. PMID: 20087185.

[36] Steele et al. Embryonic Hypotaurine Levels Contribute to Strain-Dependent Susceptibility in Mouse Models of Valproate-Induced Neural Tube Defects. Front Cell Dev Biol. 2022 Feb 21;10:832492. doi: 10.3389/fcell.2022.832492. PMID: 35265619; PMCID: PMC8898900; Lundberg et al. Mapping a chromosomal locus for valproic acid-induced exencephaly in mice. Mamm Genome. 2004 May;15(5):361-9. doi: 10.1007/s00335-004-2345-9. PMID: 15170225.

Regarding points 3.viii on pages 3-4 of Dr. Chung's report, "Many of the observational epidemiological studies on acetaminophen and the potential increased risk of ASD or ADHD examine behaviors or symptoms that are not reliable surrogates for these neurodevelopmental conditions." Dr. Chung is seeking to precisely define what measures are used to characterize ADHD and ASD behaviors. Unlike many of the other half-science points in her report, this one is clever and based on her referenced data. I will note that using the more severe phenotypes and stricter guidelines for ASD also reduces the reported impact of the environmental component on phenotype variability. This was supported by Taylor et al, as reviewed above, regarding Clinical ASD, Broad ASD, and Autistic traits. Dr. Chung is supporting only genetic causes-interactions for ASD by suggesting the use of only those data that most support that model. I suggest we use the totality of the evidence.

I do not agree that we should ignore or dismiss those studies and findings that used anything less than current clinical ASD guidelines. The measures of Broad ASD or Autistic traits reported were accepted by peers to study specific traits, behaviors, or dimensions consistent with ASD. Moreover, such exclusion criteria produce a threshold that is unlikely for older studies to meet, particularly for those studies that were conducted before current guidelines were available.

Regarding genomics, Dr. Chung reports, "These massive sample sizes frequently identify genes for disease with p values smaller than a 1 in trillion chance that the result could be by chance alone." (Chung, p. 19, para. 41). That is $1x10^{-12}$(1 with 12 zeros). The sample sizes and p values sound like good models, but it is important to appreciate point gene x environment interactions provide even better models. For example, epigenetic analyses demonstrated that compared to genetic-models, gene x environment had $p = 2.22x10^{-96}$ for best fit. That is approaching 1 over a googol (10^{-100}) chance that the result is a better fit than by chance alone. Even the additive gene + environment model shows $p = 4.78x10^{-80}$ as a better fit compared to the genetic only model.[37] For clarity, these p-values are not the probability that the null hypothesis is true, they represent the probability of observing the result assuming the null hypothesis is true. The best approximation of scientific truth is not genetics alone, that is about as far from the truth as possible, other-than *the environment alone*. The best models for phenotype, epigenetic, or disease variability are and will remain gene-environment interactions for the foreseeable future. The same is true for understanding or building models from genome wide association studies (GWAS). The best model for ASD and ADHD GWAS associations were also reported to be gene-environment interactions, based on nominal significant GWAS hits for DeepSEA[38] variants and linkage disequilibrium proxies.[37]

In paragraph 135 of her report, Dr. Chung comments, "Further, extrapolating from the large doses used in most rodent studies to humans is challenging." (Chung, p. 72, para. 135) The idea that doses used in animal models are high is prevalent among the Defendants' expert reports. I provided

[37] Czamara et al. Integrated analysis of environmental and genetic influences on cord blood DNA methylation in new-borns. Nat Commun. 2019 Jun 11;10(1):2548. doi: 10.1038/s41467-019-10461-0. PMID: 31186427; PMCID: PMC6559955.

[38] DeepSEA is a deep neural network pretrained with DNase-seq and ChIP-seq data from the ENCODE39 project and predicts the presence of histone marks, DNase hypersensitive regions, or transcription factor binding for a given 1kb sequence.

the FDA Guidance for estimating Human Equivalent Dosing (HED) from animal doses, as referenced in my report (Cabrera, p. 31, Table 1).

Regarding the criticism by Defendants' Expert Dr. Mitchell McGill that the FDA Guidance document is for selecting safe doses for humans, "The point of this process is to ensure the safety of the first clinical trial participants, not to reverse engineer a human dose back to experimental models." (McGill, pp. 10-11, para. 20-21). While the FDA document is titled, *Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers,* the estimates and conversions still produce a human equivalent dose. By definition,

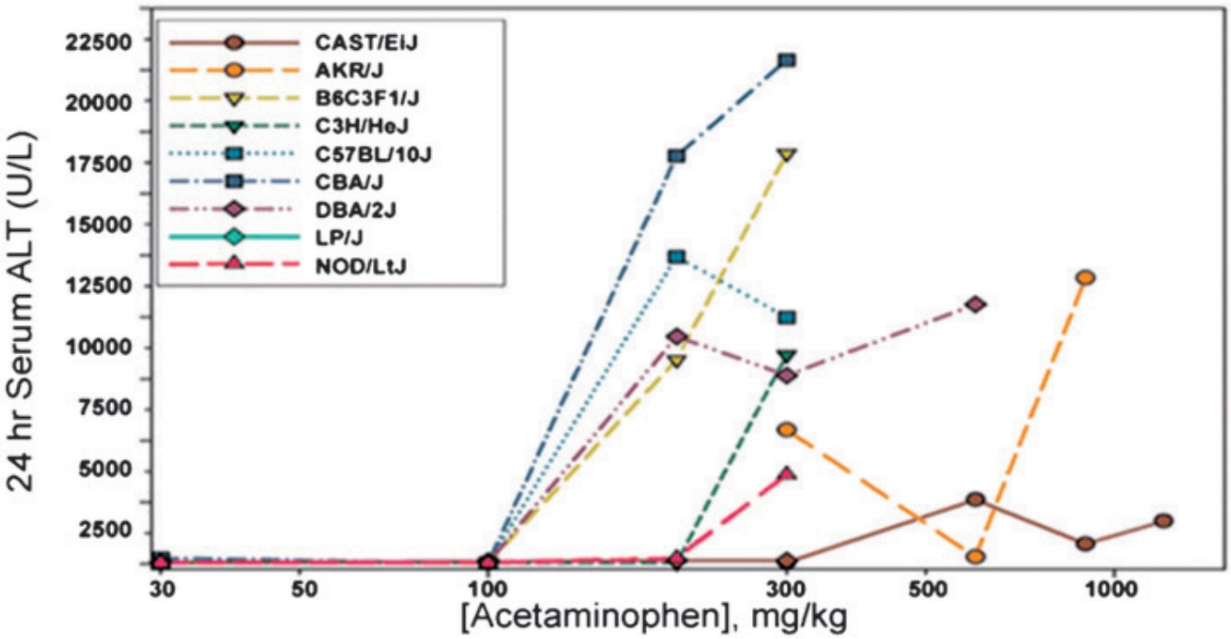
> Human equivalent dose (HED): A dose in humans anticipated to provide the same degree of effect as that observed in animals at a given dose. In this guidance, as in many communications from sponsors, the term HED is usually used to refer to the human equivalent dose of the NOAEL. When reference is made to the human equivalent of a dose other than the NOAEL (e.g., the PAD), sponsors should explicitly and prominently note this usage.

The conversion is not tissue-specific, although tissue-specific conversions are the subject of other scaling factors used by the US EPA. The conversion is based on the NOAEL, unless otherwise indicated. As indicated in my report (Cabrera, p. 34):

> Actual therapeutic doses have been determined experimentally in animals for various antinociceptive, pain relief, effects. For example, a therapeutic mouse median effective dose (ED50) is 185.52 mg/Kg (electrical tail stimulation in mice), and a therapeutic rat ED50 is 154.8 mg/Kg (Randall-Selitto's test in rats). In this example, the electrical tail stimulation test in mice is within 10% of the calculated mouse HED and the Randall-Selitto's test (paw pressure test) is within 50% of the rat HED. Similarly, the mouse ED50 of 186mg/Kg divided by 12.3 = 15.1mg/Kg (HED) and the rat ED50 of 155mg/Kg divided by 6.2 = 25mg/Kg (HED), and the package information is 16.7mg/Kg (actual human dose). Remarkably, a human dose is between the experimentally determined median effective doses from these animal models converted to HEDs 15.1-25mg/kg. Based on these data and calculations, a mouse dose of ~150-200mg/Kg or a rat dose of ~100-150 mg/Kg is therapeutic, as reported from experimental studies and calculated using HED conversions.

As I indicated, when I indicate a "therapeutic" dose, I am referencing the effective dose (ED50) for mice and rats. Additionally, these doses are good estimates for a "therapeutic" dose in humans using HED scaling. There is no safety factor applied because we are dealing with known entities. The safety factor is not applied, because a safety factor is safety from the unknown, but the actual scaling is based on the biology/allometry/mg/m^2 conversion. There is data that indicates the ED50 in mice can overlap with increased ALT or AST levels depending on the mouse strain/genetic (**Principle #1)**. I have reproduced the figure from Harrill et al. (2009) demonstrating that some mice elevate ALT at concentrations as low as 150mg/Kg, while others only above 300mg/Kg. Harrill et al. also demonstrate that at 300mg/Kg, one mouse strain (CAST/EiJ) has no necrosis and

no elevation of ALT, while at the other end of the scale, a different mouse strain (B6C3F1/J) has elevated ALT and necrosis.[39]



ALT Elevation with Acetaminophen Treatment in Mice. Mice were treated with acetaminophen via oral gavage. Figure 2F from Harrill et al. (2009)

Reported ALT or AST elevations are not grounds for excluding studies, but they do identify those studies where maternal toxicity may interact with an adverse outcome. Monitoring animal health and liver enzymes also highlights those studies that used therapeutic or low doses, below the therapeutic HEDs or ED50s, and still demonstrated developmental and/or reproductive toxicity.

Regarding an ALT and/or AST increase, the upper therapeutic daily human dose (4g/24hrs) is close to the toxic daily dose (>7g / 24hrs) for acetaminophen, so there is no mystery as to why (1) acetaminophen is the leading cause of liver failures in the US (some intentional others not) and (2) some animal studies/doses also show signs of elevated liver enzymes.

Researchers do increase the dose of medications or chemical exposures in animal models to increase the frequency of a rare event. If birth defects or neurobehavioral disorders occur at a low rate at a low dose, increasing the dose may increase the incidence of the event, which allows reasonably sized experiments to be designed. Making rare-adverse events more frequent is often a function of increasing exposure levels. Though Defendants' experts claim this as a criticism; it is basic toxicology and teratology. As indicated in my report (Cabrera, p. 184),

> **(Wilson's) Principle #6**: *Manifestations of deviant development increase in frequency and degree as dosage increases from the No Observable Adverse Effect Level (NOAEL) to* a *dose producing 100% Lethality (LD100).* This means that as you increase the concentration

[39] Harrill et al. Mouse population-guided resequencing reveals that variants in CD44 contribute to acetaminophen-induced liver injury in humans. Genome Res. 2009 Sep;19(9):1507-15. doi: 10.1101/gr.090241.108. Epub 2009 May 5. PMID: 19416960; PMCID: PMC2752130.

> of the drug exposure, you might expect to find a higher prevalence of malformed infants and that the severity of the malformations might also be expected to increase in severity with increasing dosage.

The animal models display core behaviors for ASD and ADHD, because *in utero* exposure to acetaminophen causes changes in the animal behavior consistent with ASD and ADHD. The mechanisms I have presented are published AOPs. Acetaminophen produces oxidative damage, and even at therapeutic dosages in humans, GSH levels are impacted. This was reviewed in my report (p. 61-63), such that single dose of 1 gram every six hours in humans results in changes in gene expression consistent with an oxidative stress response.[40] A single 4-gram dose, upper daily limit of intake, produces the same oxidative stress response in humans.[41] Are there risks for causing oxidative stress in humans? The answer is a resounding yes. These gene expression responses coincide with a decrease in serum total antioxidant capacity. This was demonstrated by Nuttal et al., where otherwise healthy subjects (nine men, six women) consumed a therapeutic intake of acetaminophen, 1 gram four times daily for two weeks.[42] Pharmacokinetics were studied and indicated that at therapeutic concentrations in humans (3–5 mg/L), total antioxidant levels are decreased by acetaminophen. As indicated in my report (p. 91, 117), and supported by human and animal models, pregnant women,[43] pregnant rats,[44] and pregnant mice[45] are at increased risk of oxidative damage and toxicity due to acetaminophen exposure.

Dr. Chung reports, "A meta-analysis of prenatal antidepressant exposure and offspring ASD showed significant increased risks in population-based studies (n=7 studies); however, these associations attenuated to the null in a meta-analysis of sibling-controlled studies (n=4 studies) (Vega 2020)." (Chung, p.32, para. 78). In response, I defer to the criticisms of sibling-controlled studies prepared by Andrea Baccarelli, MD, PhD, and I will also note that it is generally understood that such studies can bias from non-shared confounders and can have attenuation of associations due to random measurement error.[46] In addition, I am reminded that Carter and Blizzard reported

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[40] Jetten et al. 'Omics analysis of low dose acetaminophen intake demonstrates novel response pathways in humans. Toxicol Appl Pharmacol. 2012 Mar 15;259(3):320-8. doi: 10.1016/j.taap.2012.01.009. Epub 2012 Jan 20. PMID: 22285215.

[41] Fannin et al. Acetaminophen dosing of humans results in blood transcriptome and metabolome changes consistent with impaired oxidative phosphorylation. Hepatology. 2010 Jan;51(1):227-36. doi: 10.1002/hep.23330. PMID: 19918972; PMCID: PMC2925683.

[42] Nuttall et al. The impact of therapeutic doses of paracetamol on serum total antioxidant capacity. J Clin Pharm Ther. 2003 Aug;28(4):289-94. doi: 10.1046/j.1365-2710.2003.00493.x. PMID: 12911681.

[43] Li et al. Urinary paracetamol (4-acetaminophenol) and its isomer 2-acetaminophenol of Chinese pregnant women: Exposure characteristics and association with oxidative stress biomarkers. Sci Total Environ. 2022 Dec 15;852:158375. doi: 10.1016/j.scitotenv.2022.158375. Epub 2022 Aug 29. PMID: 36049689.

[44] Lin and Levy. Effect of pregnancy on the pharmacokinetics of acetaminophen in rats. J Pharmacol Exp Ther. 1983 Jun;225(3):653-9. PMID: 6602874.

[45] Larrey et al. Effects of pregnancy on the toxicity and metabolism of acetaminophen in mice. J Pharmacol Exp Ther. 1986 Apr;237(1):283-91. PMID: 3083096.

[46] Frisell et al. Sibling comparison designs: bias from non-shared confounders and measurement error. Epidemiology. 2012 Sep;23(5):713-20. doi: 10.1097/EDE.0b013e31825fa230. PMID: 22781362.

that both acetaminophen and antidepressants (fluoxetine, sertraline, paroxetine, and citalopram) showed significant enrichment for interactions with autism susceptibility genes (ASGs).[47]

In response to paragraph 105 (pp. 49-51) and paragraph 122 (pp. 63-64) of Dr. Chung's report, Dr. Chung summarizes in the latter, "Partner's (paternal) use of acetaminophen was associated with ADHD or other behavioral outcomes in children in both studies where it was analyzed (Stergiakouli 2016, Ystrom 2017). Indeed, the risk estimates were higher for paternal than for maternal exposure, and there was evidence of dose response. This suggests that genetic/familial factors are likely to be confounding any associations observed between prenatal exposure to acetaminophen and ADHD." (Chung, p. 63, para. 122). I disagree, this does not suggest genetic/familial factors are confounding. The simplest and biologically relevant explanation for this observation is that acetaminophen is a reproductive toxin in males and females. Specifically, acetaminophen toxicity is treated with N-acetylcysteine because it restores GSH, and acetaminophen is known to deplete this important and essential antioxidant. Multiple Defendants' experts suggest that toxicity only occurs in the liver, or only at high dosages, and while the liver is a target organ for toxicity due to its ability to metabolize acetaminophen into NAPQI, so too are the reproductive organs. In men of child-bearing age, the US National Institutes of Health (NIH) reported that acetaminophen metabolites in urine were associated with DNA oxidation and DNA fragmentation in sperm.[48] It is not just NAPQI, as it has also been shown clinically that the acetaminophen metabolite AM404 produced via FAAH interferes with human sperm Ca2+-signaling.[49] The NIH clinical study was published concurrently with Ystrom et al, both in November 2017, so neither could make the direct connection at the time, but juxtaposed next to each other, they provide evidence of reproductive toxicity in men taking "therapeutic" doses of acetaminophen. While paternal impacts are beyond the scope of *in utero* exposures, there is similar evidence of reproductive toxicity maternally.

Examining the impact of acetaminophen on female gametes cannot be determined without invasive treatments or procedures, but fetal human ovaries in culture have been tested for acetaminophen-induced adverse-drug interactions.[50] This study reported that clinically relevant concentrations of acetaminophen (10^{-8} to 10^{-3} M) are metabolized by human fetal ovaries, with notable toxicities in ovaries at the 10-12 week developmental (DW) state. This timing is important because cytotoxicity is likely at the highest concentrations 10^{-3} M, but the differences in toxicity at lower dosages by developmental stage are consistent with a critical window of developmental and reproductive toxicity. This includes no significant impacts at 7 DW or 8-9 DW on ovarian cell number, and a significant decrease at concentrations as low as 10^{-7} (100nM) in 10-12 DW cells. The proportion

[47] Carter and Blizard. Autism genes are selectively targeted by environmental pollutants including pesticides, heavy metals, bisphenol A, phthalates and many others in food, cosmetics or household products. Neurochem Int. 2016 Oct 27:S0197-0186(16)30197-8. doi: 10.1016/j.neuint.2016.10.011. Epub ahead of print. PMID: 27984170.

[48] Smarr et al. Male urinary paracetamol and semen quality. Andrology. 2017 Nov;5(6):1082-1088. doi: 10.1111/andr.12413. Epub 2017 Aug 29. PMID: 28853221.

[49] Rehfeld et al. Human sperm cells can form paracetamol metabolite AM404 that directly interferes with sperm calcium signalling and function through a CatSper-dependent mechanism. Hum Reprod. 2022 May 3;37(5):922-935. doi: 10.1093/humrep/deac042. PMID: 35259261.

[50] Lecante et al. Acetaminophen (APAP, Paracetamol) Interferes With the First Trimester Human Fetal Ovary Development in an Ex Vivo Model. J Clin Endocrinol Metab. 2022 May 17;107(6):1647-1661. doi: 10.1210/clinem/dgac080. PMID: 35147701; PMCID: PMC9113793.

of dying ovarian cells was also higher at 10-12 DW compared to 7-9 DW (as indicated in Figure 1, Lecante et al.). It is also worth mentioning that some of the dose effects are U-shaped in the study, where parts of the clinical range 10^{-7} to 10^{-5} have significant and stronger impacts compared to concentrations both higher or lower, while the highest concentration 10^{-3} shows extreme/overt cytotoxicity. For example, the number of germ cells decreased in 10-12 DW cells at 10^{-7} and 10^{-5}-10^{-3} concentrations, germ cell density also decreased at 10^{-8}- 10^{-6} and 10^{-4}- 10^{-3}, but earlier developmental stages were generally less sensitive. This study provides additional supportive evidence for the reproductive toxicity of acetaminophen at relevant clinical concentrations in human fetal ovaries and also reported disruption in endocrine metabolites, including changes in progesterone, 17α-hydroxyprogesterone (17-OHP), and prostaglandin estradiol (E2). In animal models, similar paternal and maternal reproductive toxicity endpoints have also been observed. Even at the low dosing (30mg/Kg) in mice, reproductive toxicity was observed.[51]

The reported DNA oxidation, DNA fragmentation, and decreased gametic proliferation associated with and caused by acetaminophen are important regarding fertility. This damage is also important regarding the genetics of offspring, not as genetic confounding, but via DNA-oxidation causing mutations in gametes, some being deleterious *de novo* mutations, that would thereby become associated with an increased risk of ASD after fertilization and embryonic development. Specifically, Pugsley et al.[52] examined studies regarding the hypothesis: environmental exposures associated with an increased risk of ASD are causal in the occurrence of deleterious de novo mutations. The authors conducted a review of epidemiological evidence and the mutagenic/genotoxic potential of various environmental agents, including heavy metals, such as mercury, medications, including acetaminophen, and drugs of abuse, including cannabis, all of which have been associated with ASD risk. They propose three potential mechanisms through which environmental, industrial, or pharmaceutical agents could lead to genomic alterations: direct interaction with genetic material, interference with endogenous DNA repair, and oxidative DNA damage. Support for the hypothesis includes Smarr et al. (NIH),[48] reporting "the elevated concentration of urinary paracetamol is associated with increased DNA fragmentation in human sperm *in vivo*."

On pages 71-72 of her report, Dr. Chung states, "I am also not aware that the referenced biological pathways are established or accepted by the medical and scientific community as causal mechanisms for ASD or ADHD." (Chung, pp.71-72, para. 141). I have referenced published adverse outcome pathways (AOPs) in my expert report. These include "Binding of electrophilic chemicals to SH(thiol)-group of proteins and /or to seleno-proteins involved in protection against

[51] Rossitto et al. In utero exposure to acetaminophen and ibuprofen leads to intergenerational accelerated reproductive aging in female mice. Commun Biol. 2019 Aug 13;2:310. doi: 10.1038/s42003-019-0552-x. PMID: 31428698; PMCID: PMC6692356; Rossitto et al. Intergenerational effects on mouse sperm quality after in utero exposure to acetaminophen and ibuprofen. FASEB J. 2019 Jan;33(1):339-357. doi: 10.1096/fj.201800488RRR. Epub 2018 Jul 6. PMID: 29979629.

[52] Pugsley et al. Environmental exposures associated with elevated risk for autism spectrum disorder may augment the burden of deleterious de novo mutations among probands. Mol Psychiatry. 2022 Jan;27(1):710-730. doi: 10.1038/s41380-021-01142-w. Epub 2021 May 17. PMID: 34002022; PMCID: PMC8960415.

oxidative stress during brain development leads to impairment of learning and memory"[53] and "Adverse Outcome Pathway on chronic binding of antagonist to N-methyl-D-aspartate receptors (NMDARs) during brain development induces impairment of learning and memory abilities."[54] Consistent with the pathways, is also the computational model presented by Vargason et al (2017) examining the enzymes in the methionine cycle and transsulfuration pathways, the latter of which produces GSH, as models of determining ASD and neurotypical metabolic differences.[55] The authors reported that sensitivity analysis revealed the activity of the enzyme glutamate-cysteine ligase, was import for model predictions, and that this finding aligns with the formation of glutamylcysteine, the rate-limiting step in glutathione synthesis. A similar computation model was published by Howsmon et al. (2017), based on biochemical interactions between five variables (DNA methylation, 8-OHG, Glu.-Cys., fCystine/fCysteine,% oxidized glutathione).[56] Differences in these variables allowed multivariate classification of the participants as ASD or neurotypical, with 96.1% of all neurotypical participants being correctly identified, and correctly identifying 97.6% of the ASD cohort. Once again, we see that the same metabolites (e.g., 8-OHG, glutathione, oxidized glutathione) modified by acetaminophen are the same metabolites associated with ASD outcomes.

On page 73, Dr. Chung reports, "Acetaminophen is so widely taken in the general population that if there were an increased risk of DNA damage, there would have been reports of increased cancer frequency (likely of epidemic scope) in the general population of individuals who regularly take acetaminophen." (Chung, p. 73, para. 142). As indicated in my report, studies have reported statistically increased cancer risks in humans, specific to myeloid leukemia (Cabrera, p. 74).

In conclusion, it is really no surprise that gene-environment interactions explain biology better than the strictly genetic model proposed by Dr. Chung, because life is more than just DNA (deoxyribonucleic acid), RNA (ribonucleic acid), and proteins. Even if life did not have emergent properties, which it does, life must still interact with the environment to sustain itself. While there are various definitions of life, life needs the environment to sustain itself, and Dr. Chung's omission of environmental interactions, and thereby omission of acetaminophen interactions, makes her model and viewpoint incomplete. Her cited references include gene-environment interactions and outside of her expert report, even her own scientific publications and public presentations acknowledge the importance of gene-environment interactions. Gene-environment interactions

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[53] Tschudi-Monnet, F., et al. (2022), "Binding of electrophilic chemicals to SH(thiol)-group of proteins and /or to seleno-proteins involved in protection against oxidative stress during brain development leading to impairment of learning and memory", OECD Series on Adverse Outcome Pathways, No. 20, OECD Publishing, Paris, https://doi.org/10.1787/4df0e9e4-en.

[54] Sachana, M., S. Munn and A. Bal-Price (2016), "Adverse Outcome Pathway on chronic binding of antagonist to N-methyl-D-aspartate receptors (NMDARs) during brain development induces impairment of learning and memory abilities", OECD Series on Adverse Outcome Pathways, No. 5, OECD Publishing, Paris, https://doi.org/10.1787/5jlsqs5hcrmq-en.

[55] Vargason et al. Mathematical modeling of the methionine cycle and transsulfuration pathway in individuals with autism spectrum disorder. J Theor Biol. 2017 Mar 7;416:28-37. doi: 10.1016/j.jtbi.2016.12.021. Epub 2016 Dec 29. PMID: 28040439; PMCID: PMC5293619.

[56] Howsmon et al. Classification and adaptive behavior prediction of children with autism spectrum disorder based upon multivariate data analysis of markers of oxidative stress and DNA methylation. PLoS Comput Biol. 2017 Mar 16;13(3):e1005385. doi: 10.1371/journal.pcbi.1005385. PMID: 28301476; PMCID: PMC5354243.

remain the better model, for both ADHD and ASD, and environmental factors can cause and do modify risk for neurodevelopmental outcomes. Furthermore, acetaminophen can cause hepatotoxicity and neurodevelopmental toxicity, consistent with core ADHD and ASD behaviors in animals and causative of ADHD and ASD in humans due to *in utero* exposure during pregnancy.

I expressly reserve the right to amend or supplement this rebuttal report and to read, review and comment upon any reports prepared by Defendants' experts.

All opinions offered herein are held to a reasonable degree of scientific certainty.

Dated: July 28, 2023

Respectfully Submitted,

Robert M. Cabrera, Ph.D.